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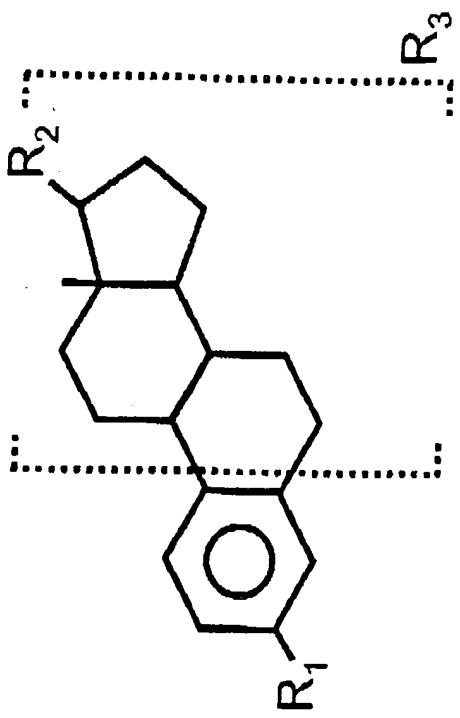


Figure 1: General structure of activators of non-genomic Estrogen-Like Signalling (ANGELS).

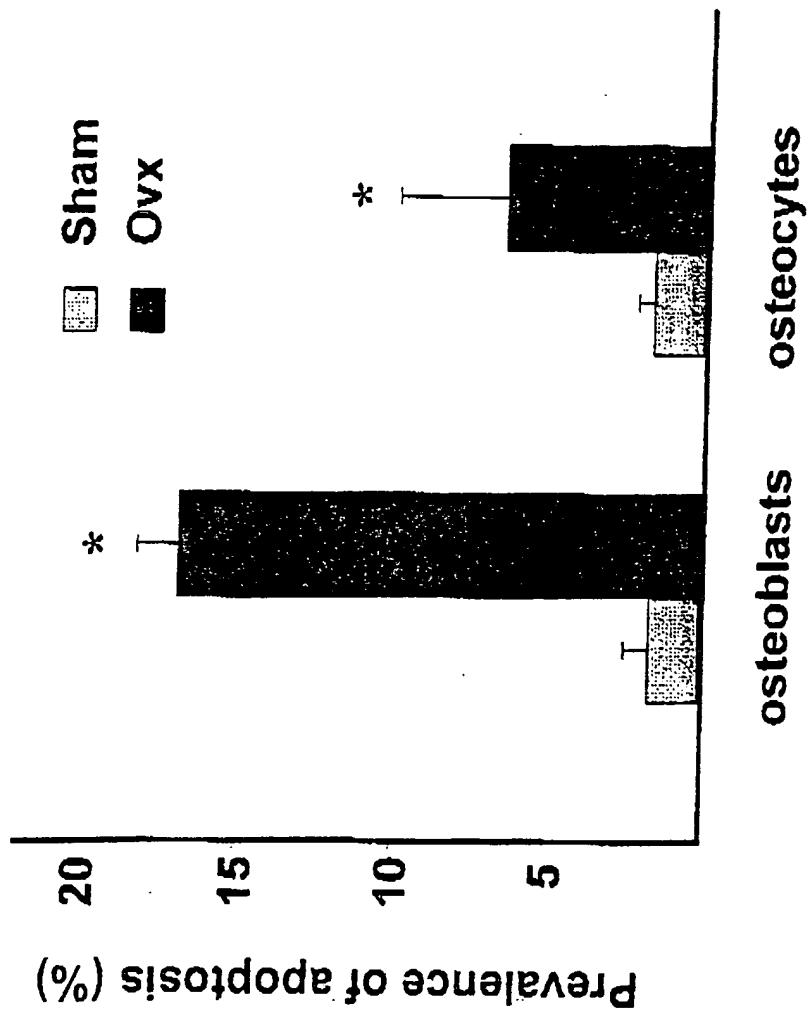


Figure 2: Estrogen deficiency causes increased apoptosis of osteoblasts and osteocytes in murine vertebral bone.

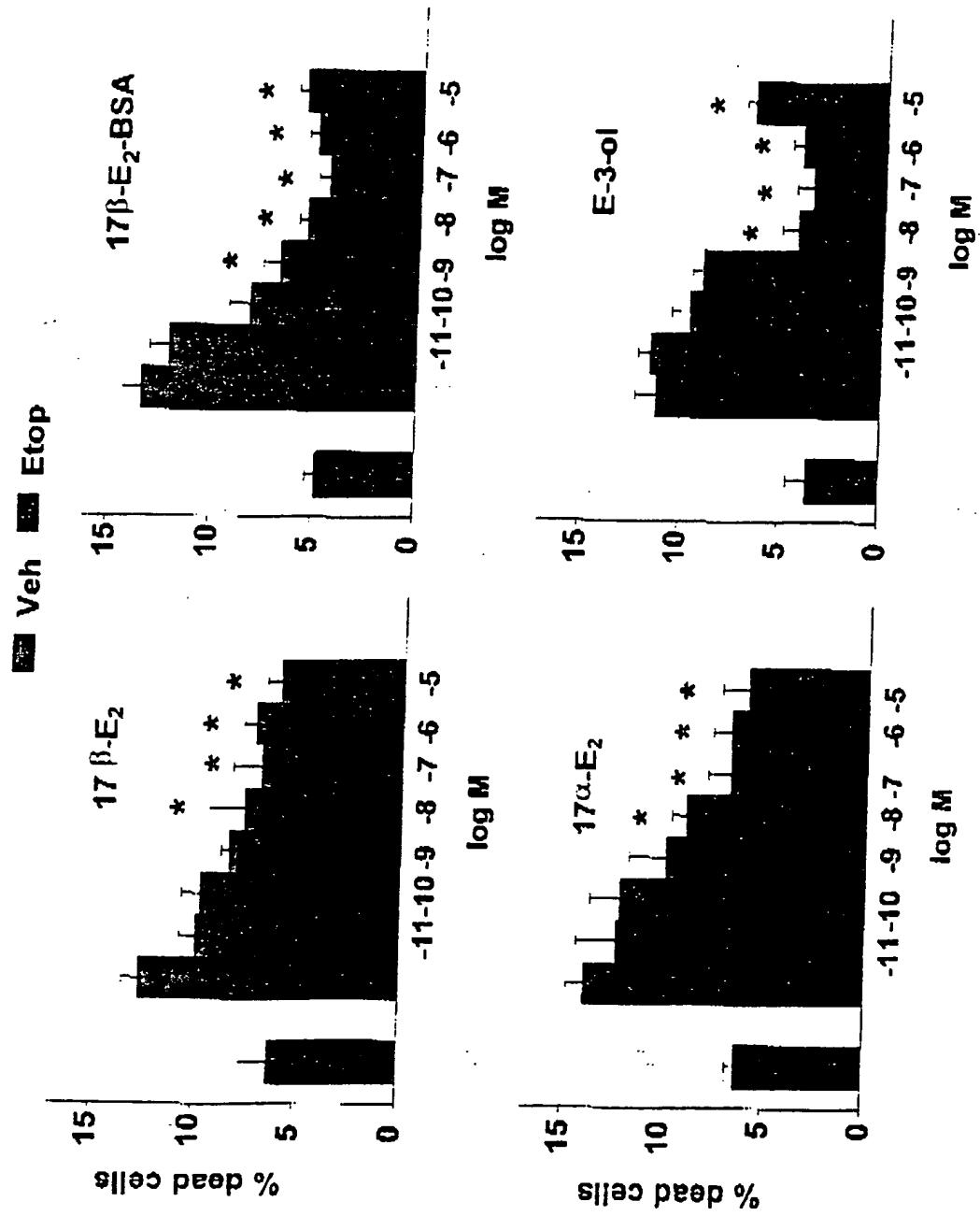


Figure 3: Inhibition of apoptosis of osteoblastic cells.

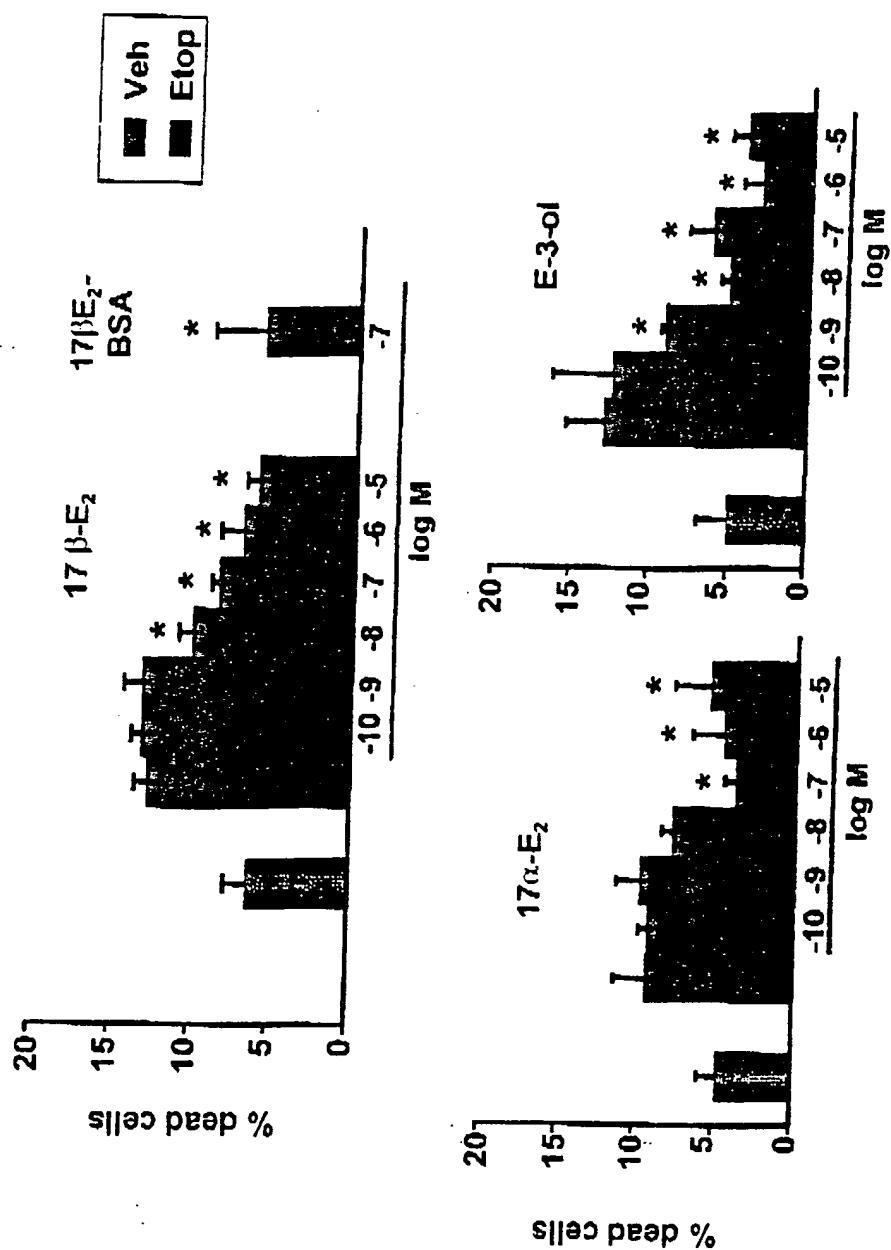


Figure 4: Inhibition of apoptosis of MLO-Y4 osteocytic cells by ANGELS

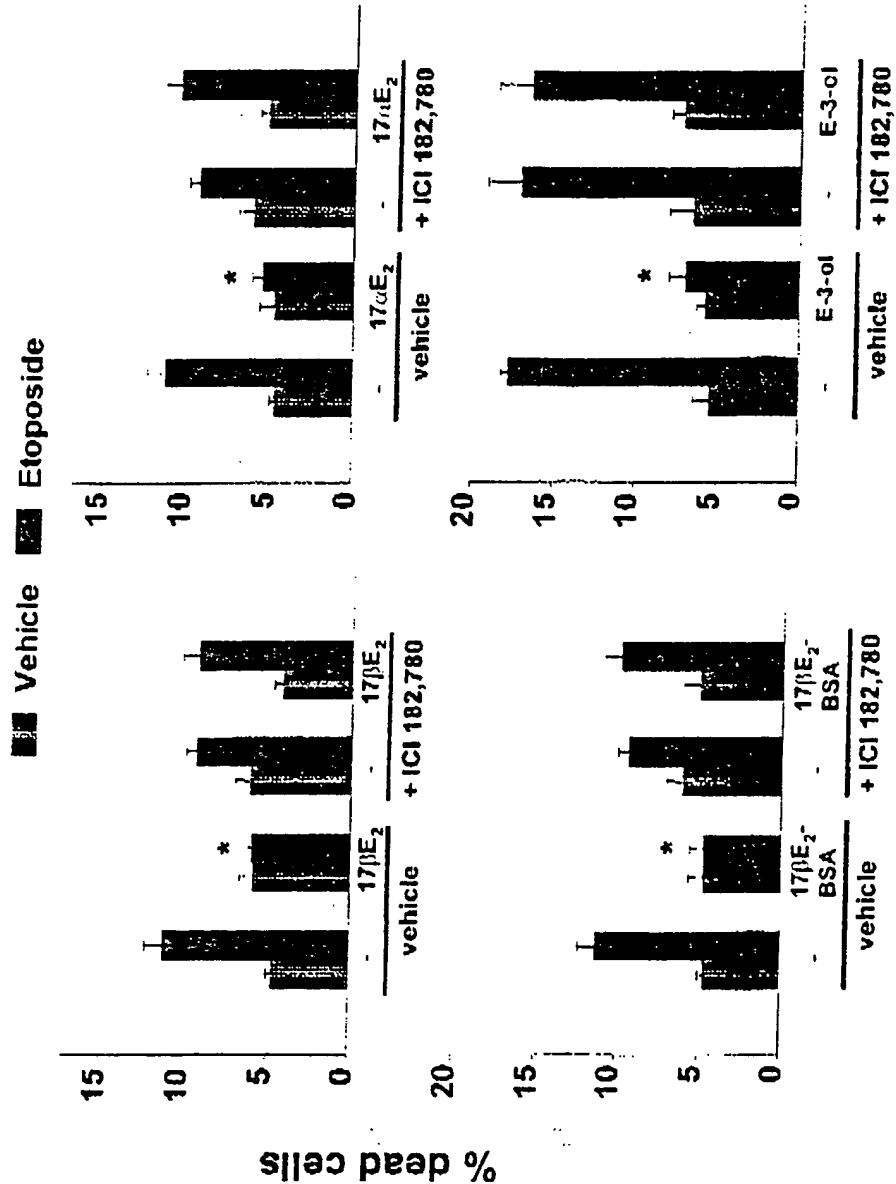


Figure 5: Blockade of the anti-apoptotic effect of estrogen and ANGELS by ICI 182,780 in osteoblastic cells

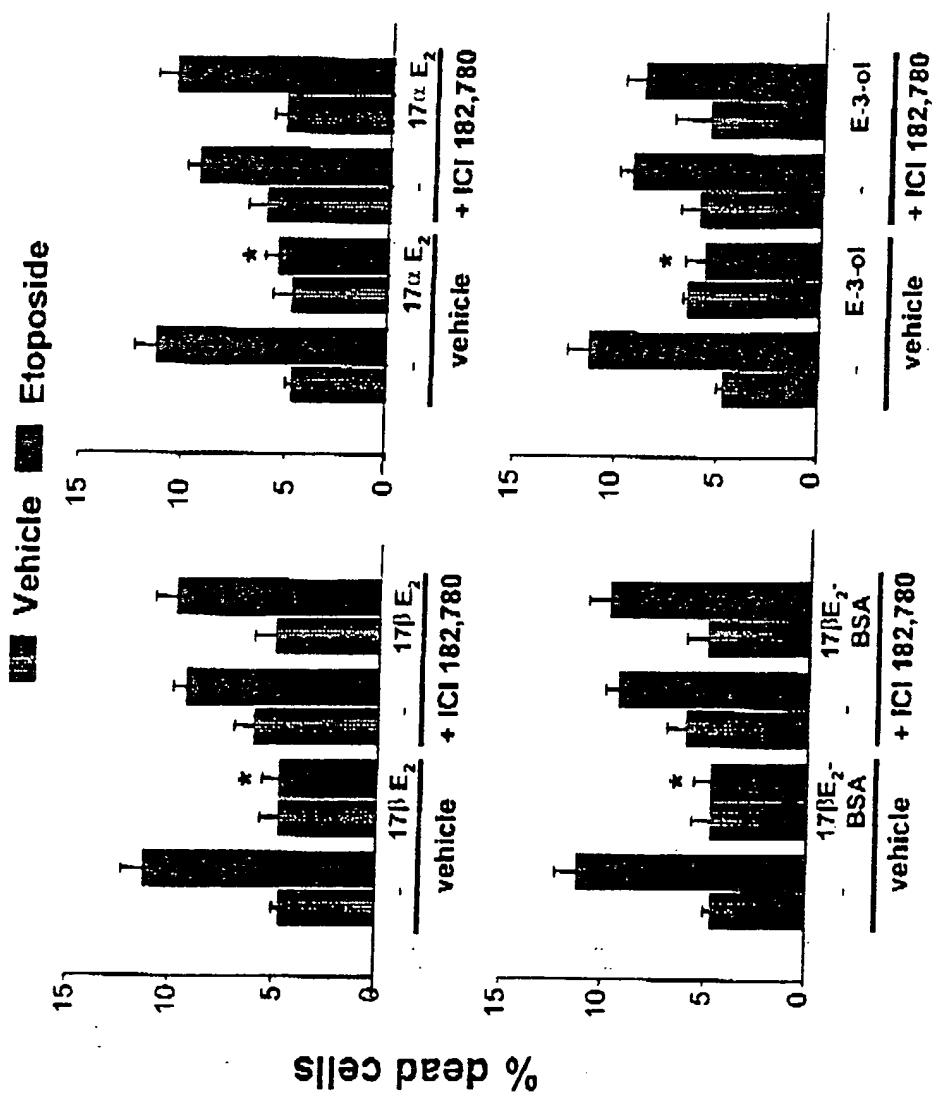


Figure 6: Inhibition of the antiapoptotic effect of estrogen and ANGELS by ICI 182,780 in MLO-Y4 osteocytic cells

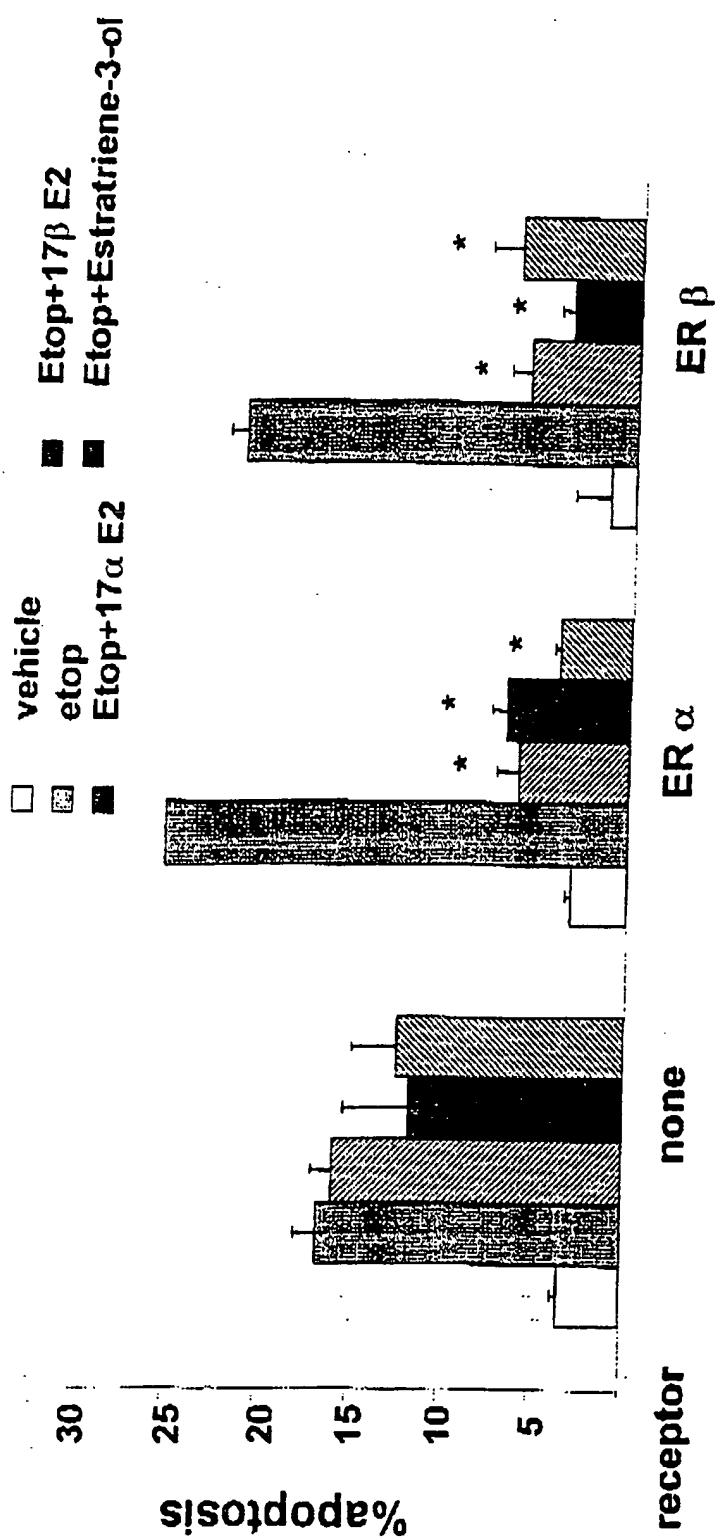


Figure 7: Estrogen receptor α or β is required for the antiapoptotic effects of 17 β estradiol, 17 α estradiol, and estratriene-3-ol on etoposide-induced apoptosis (experiment 1/21/99).

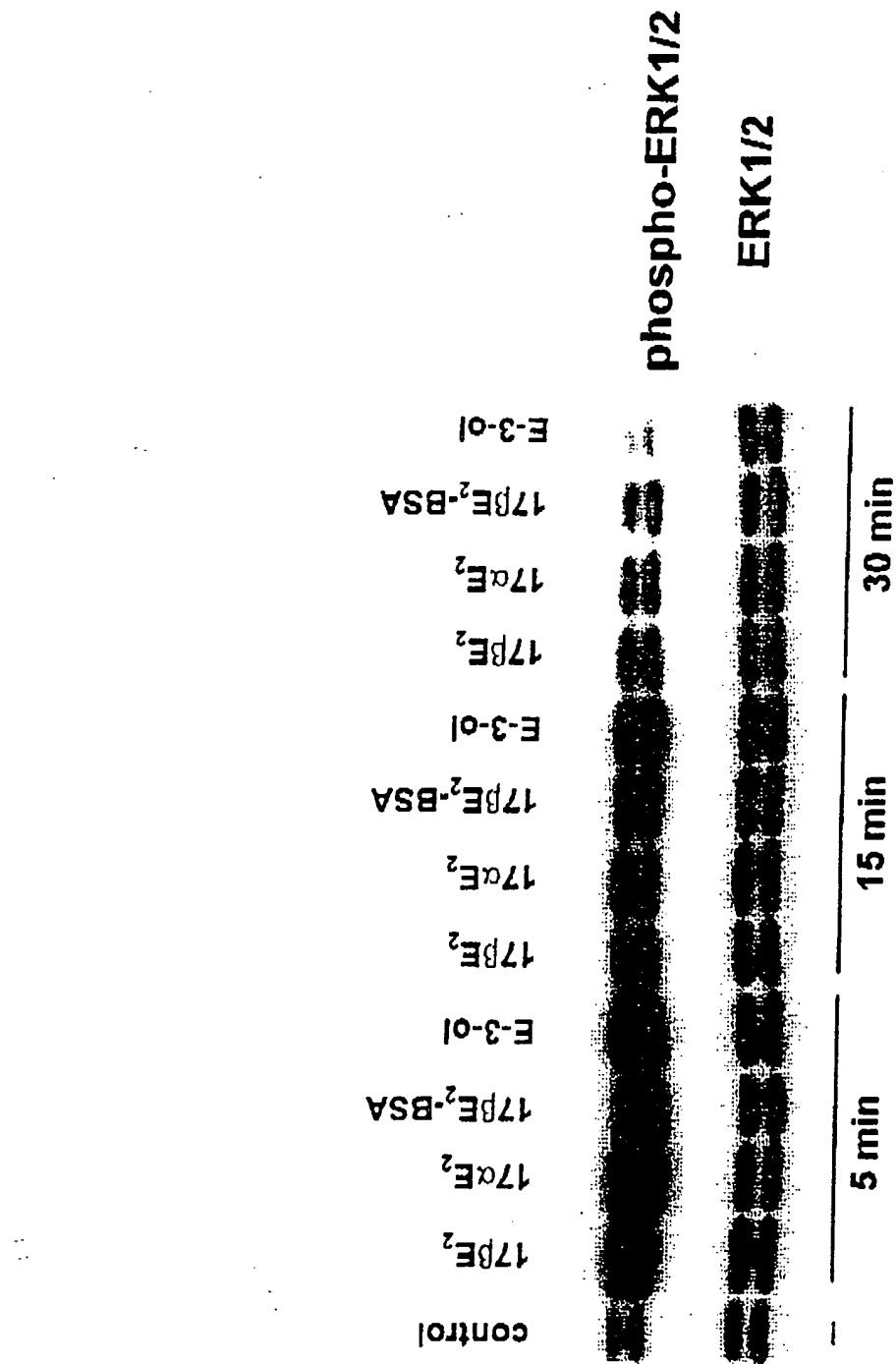


Figure 8: Activation of Extracellular Signal Regulated Kinases (ERKs)

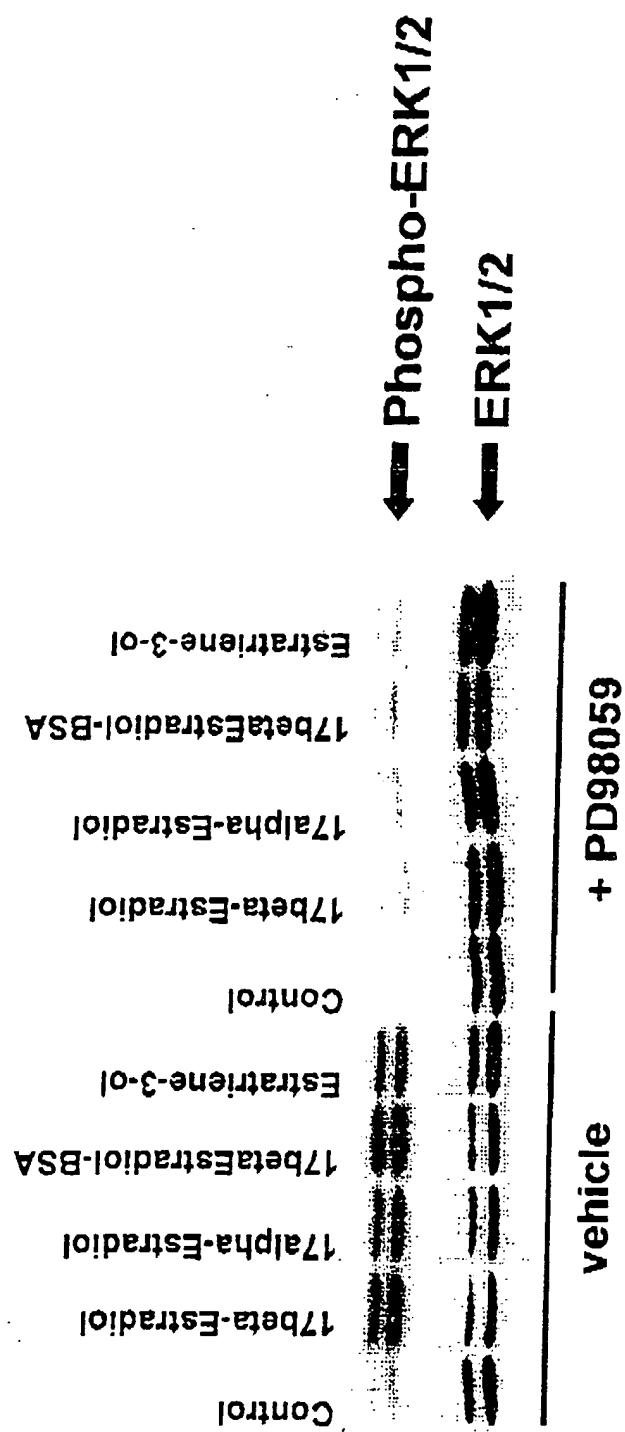


Figure 9: The effect of estrogenic compounds on the activation of ERK1/2 is blocked by a specific inhibitor.

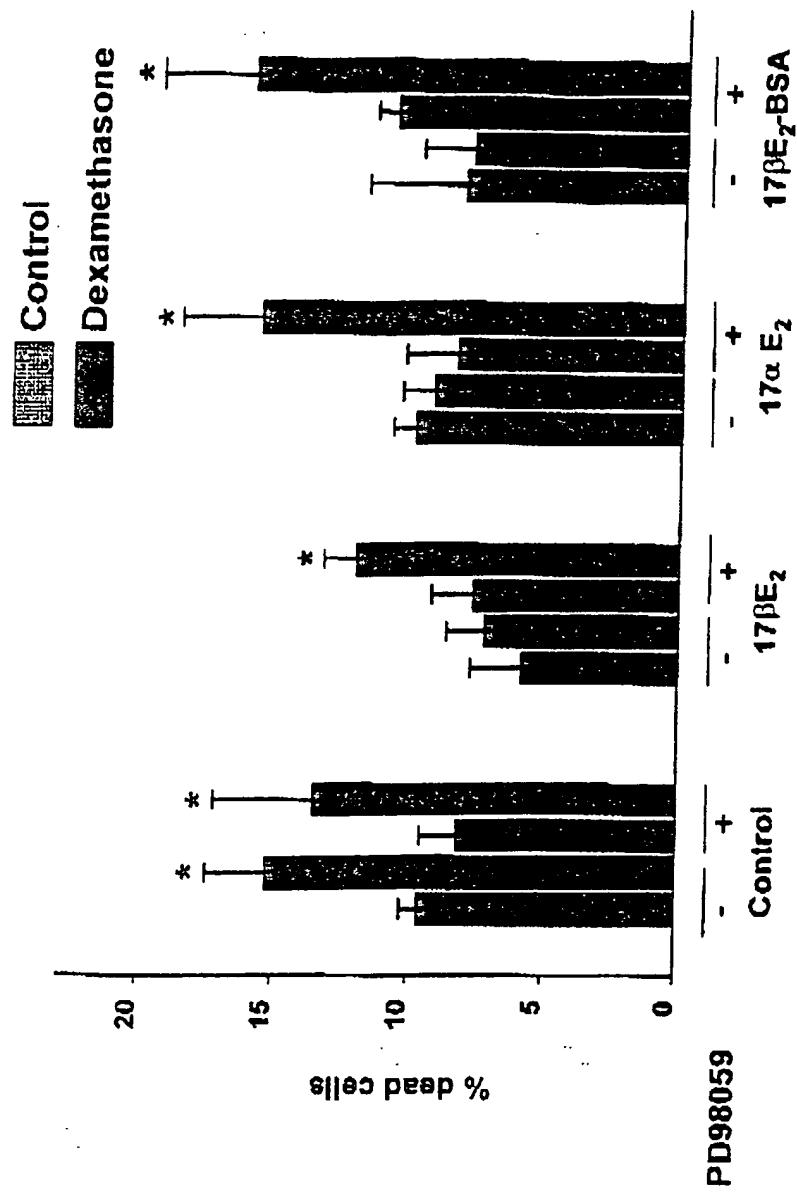


Figure 10: The specific inhibitor of ERK activation abolishes the anti-apoptotic effect of the estrogenic compounds.

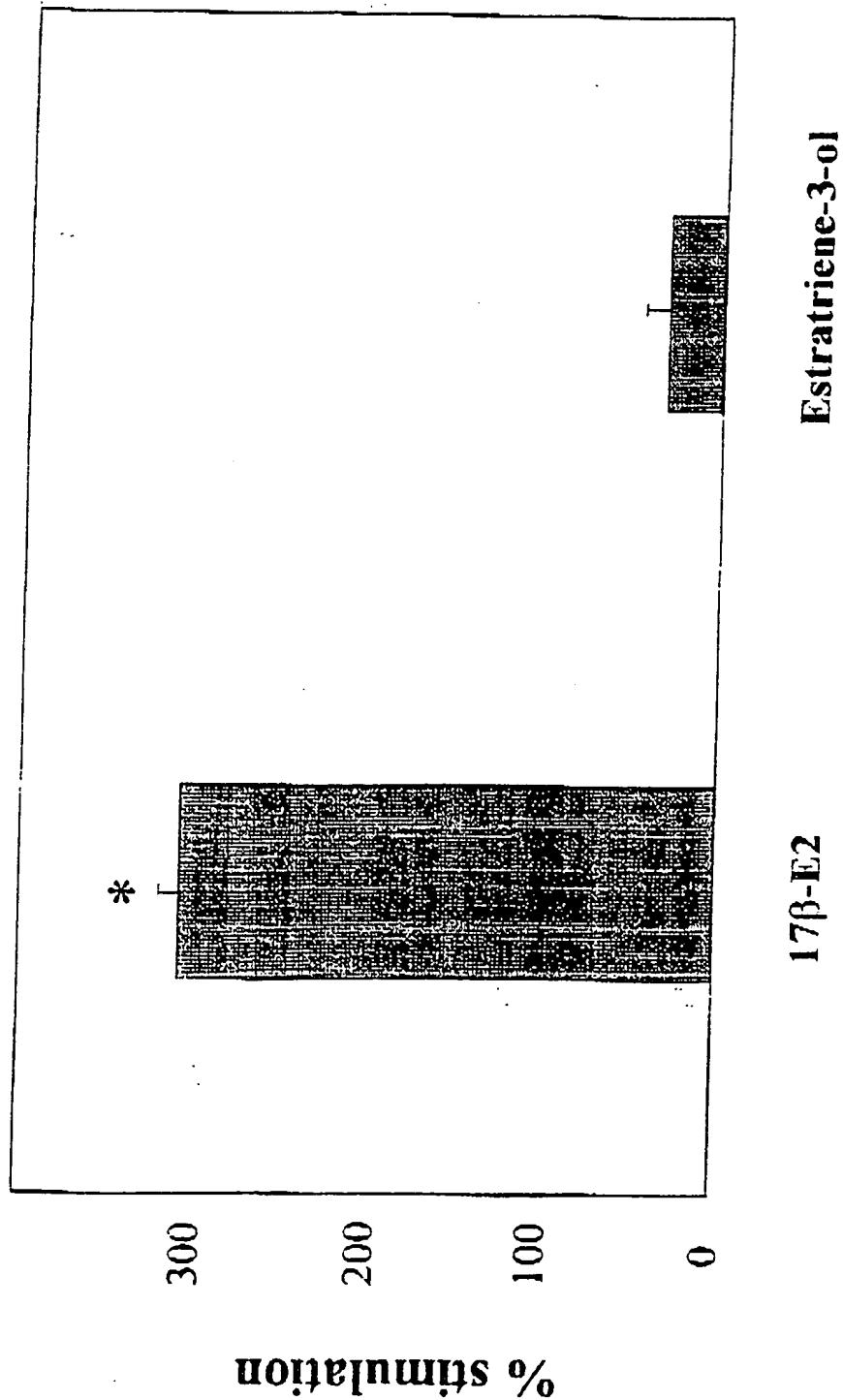
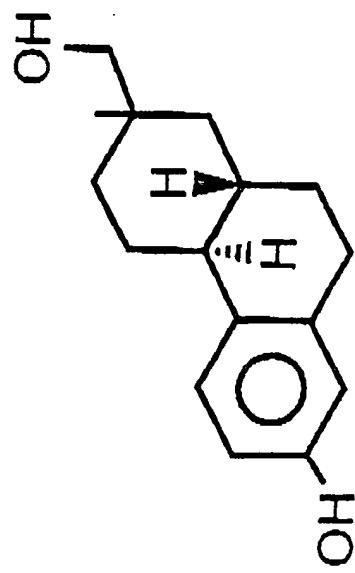
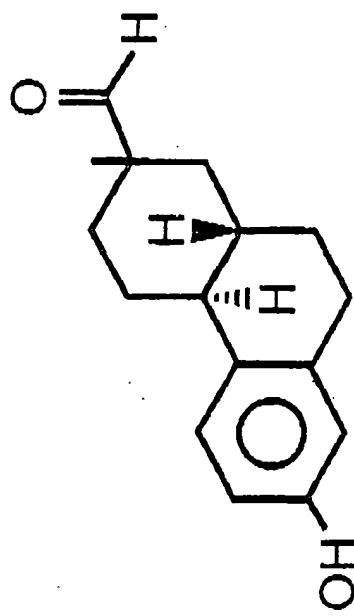


Figure 11: Unlike 17β estradiol, estratriene-3-ol does not transactivate an estrogen response element through ER α .



C₁₆H₂₂O₂
MW=246

[2S-(2a,4a α ,10a β)]-1,2,3,4,4a,9,10,10a-octahydro-7-hydroxy-2-methyl-2-phenanthrenemethanol



C₁₆H₂₀O₂
MW=244

[2S-(2a,4a α ,10a β)]-1,2,3,4,4a,9,10,10a-octahydro-7-hydroxy-2-methyl-2-phenanthrenecarboxaldehyde

Figure 12

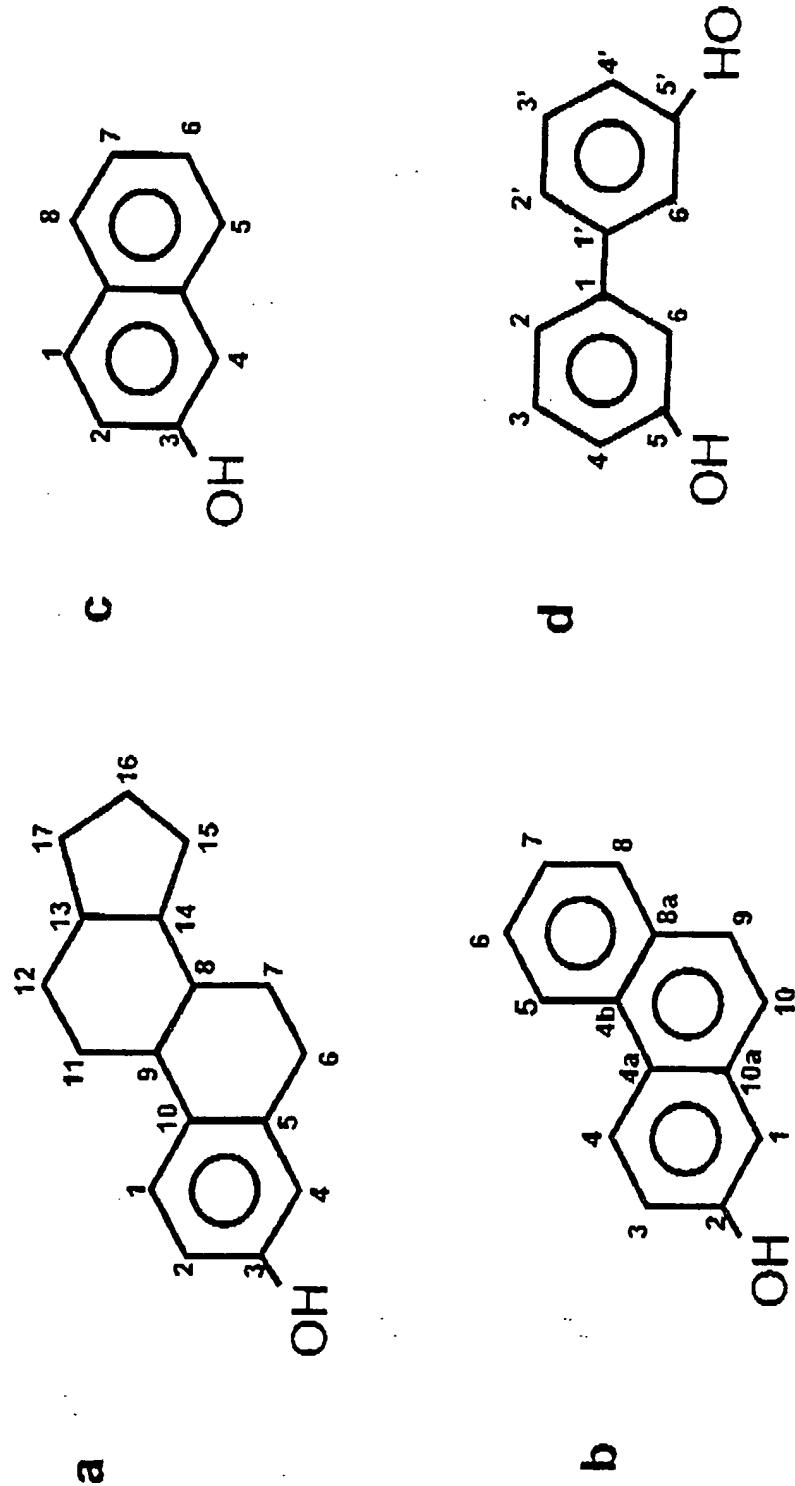


Figure 13

Docket/App No.: 3650.1006-010
Title: Methods and Compositions...
Inventors: Stavros C. Manolagas, *et al.*

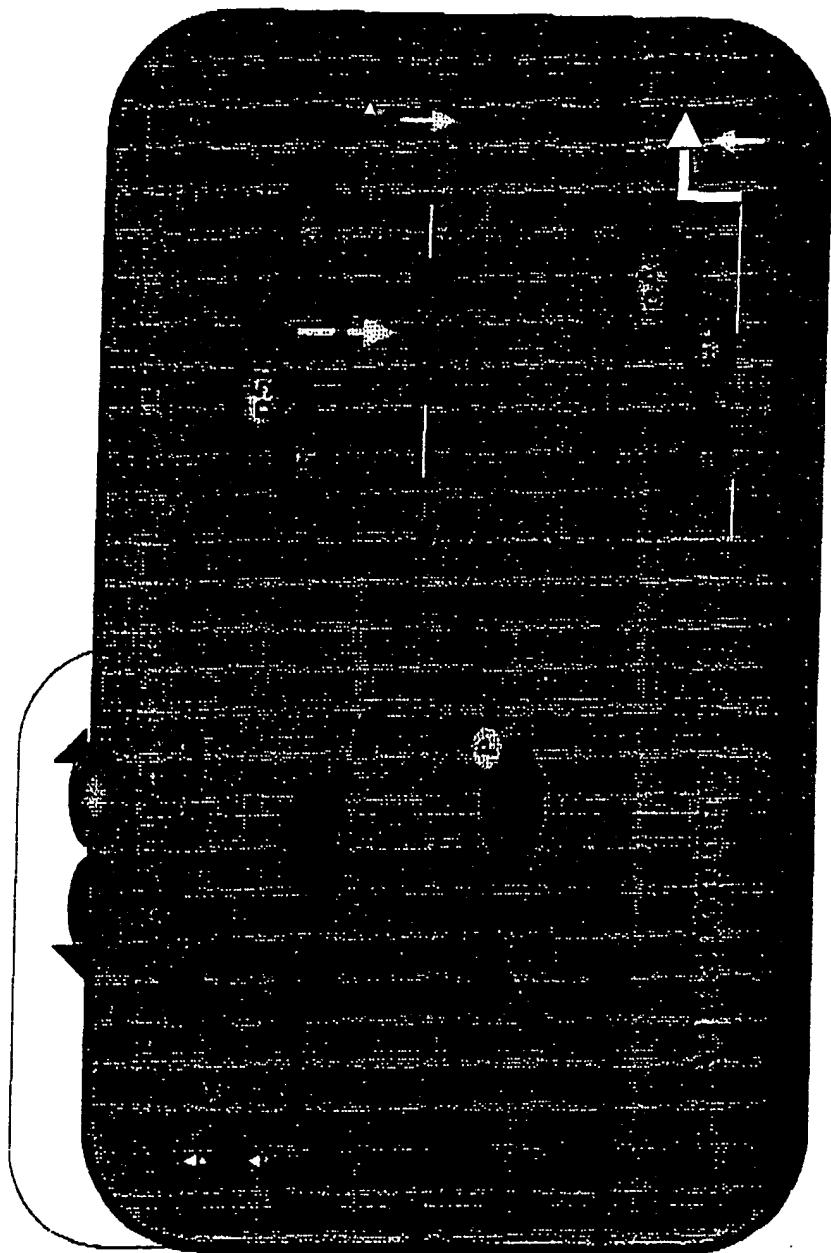
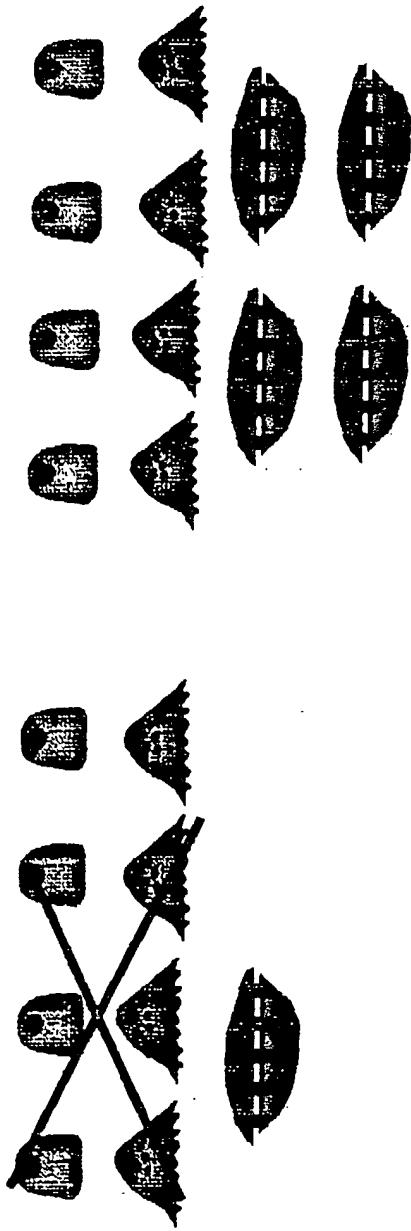


Figure 14: Mechanisms of Estrogen Receptor Action

Formation occurs only on sites of previous osteoclastic bone resorption.

Anti-resorptive Non anti-resorptive (i.e. ANGELS)



**Small and slow increase
in trabecular thickness**

**Large and rapid increase
in trabecular thickness**

**Anti-fracture efficacy
(through inhibition of osteocyte apoptosis)**

Figure 15: Implications of the effects of anti-resorptive vs. non anti-resorptive agents on apoptosis

R^1 AND/OR R^2 SUBSTITUTION:

	STRUCTURE
HYDROXY	-OH
METHYL	-CH ₃
METHYL ET	-OCH ₃
ACETYL	$\begin{array}{c} \text{O}-\text{C}-\text{CH}_3 \\ \\ \text{C} \end{array}$
ETHYL ET	$\begin{array}{c} \text{O}-\text{CH}_2-\text{CH}_3 \\ \\ \text{C} \end{array}$
J. J. (OR 1)	$\begin{array}{c} \text{OCH}_3 \\ \\ \text{OCH}_3 \end{array}$
DIMETHYL ET	$\begin{array}{c} \text{OCH}_3 \\ \\ \text{OCH}_3 \end{array}$
ETHYL-	$\begin{array}{c} \text{C}\equiv\text{CH} \\ \\ \text{C} \end{array}$
BENZYL	$\begin{array}{c} \text{O}-\text{C} \\ \\ \text{C}_6\text{H}_5 \end{array}$
BENZYL ET	$\begin{array}{c} \text{OCH}_2-\text{C} \\ \\ \text{C}_6\text{H}_5 \end{array}$
GLUCURONIC ACID	C ₆ H ₈ O ₅
SULFATE SODIUM	OSO ₃ Na
CHELATE	=
VALINE	-C ₅ H ₉ CO
CYCLOPENTYLPROPYL	$\begin{array}{c} \text{C} \\ \\ -\text{O}-\text{C}-(\text{CH}_2)_2-\text{C}_5\text{H}_5 \end{array}$
PROPIOLIC ACID	$\begin{array}{c} \text{C} \\ \\ -\text{O}-\text{C}-(\text{CH}_2)_2 \end{array}$
HEMISUCCINIC ACID	-C ₄ H ₄ O ₅
PALMITIC ACID	-C ₁₆ H ₃₂ O ₂

Figure 16A

R₁ AND/OR R₂ SUBSTITUTIONS

STRUCTURE

SODIUM PHOSPHATE -O-PO₃Na₂

ENANTHIDE -C₇H₁₂O

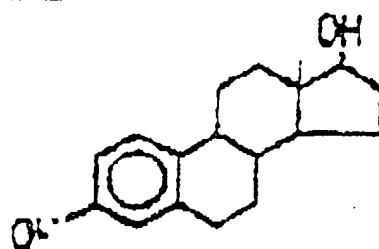
GLUCURONIDE SODIUM Salt -C₆H₈O₆Na

STEARATE -C₁₈H₃₄O

TERTIARY AMMONIUM SALT -N-(C₂H₅)₃

CYPICOLIC ACID

17b ESTER



17a ESTER

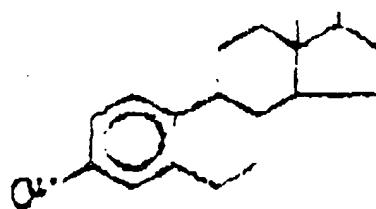


Figure 16B

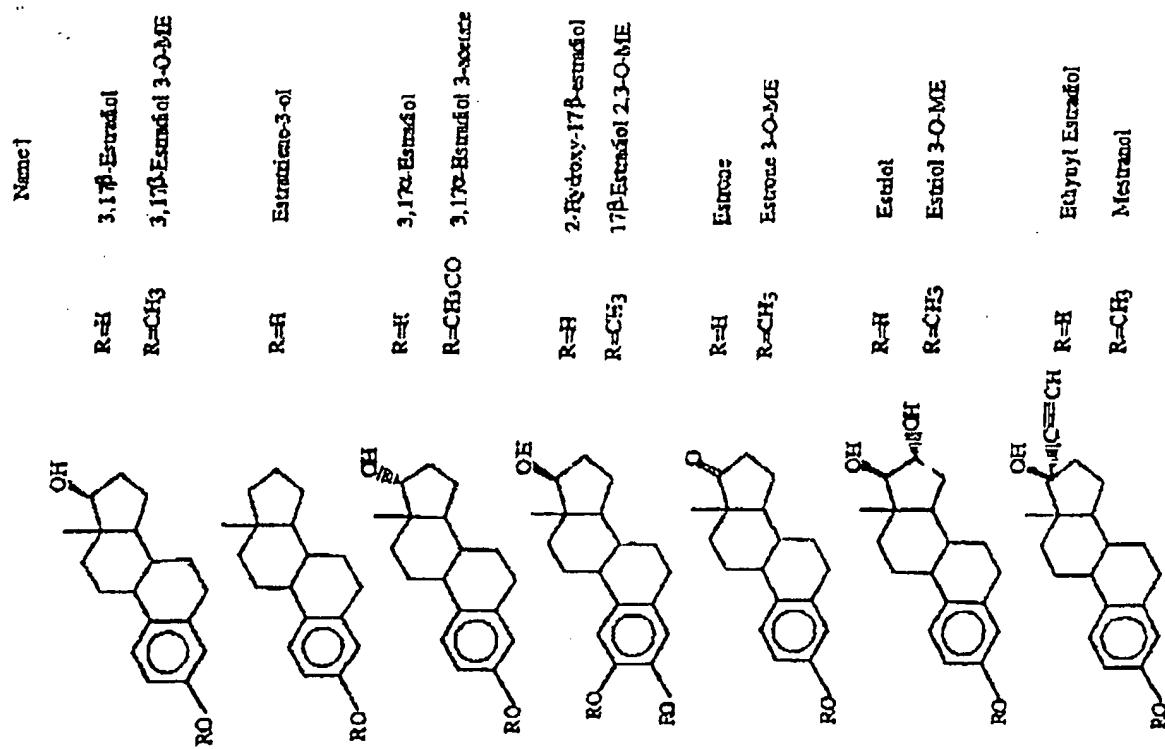


Figure 17

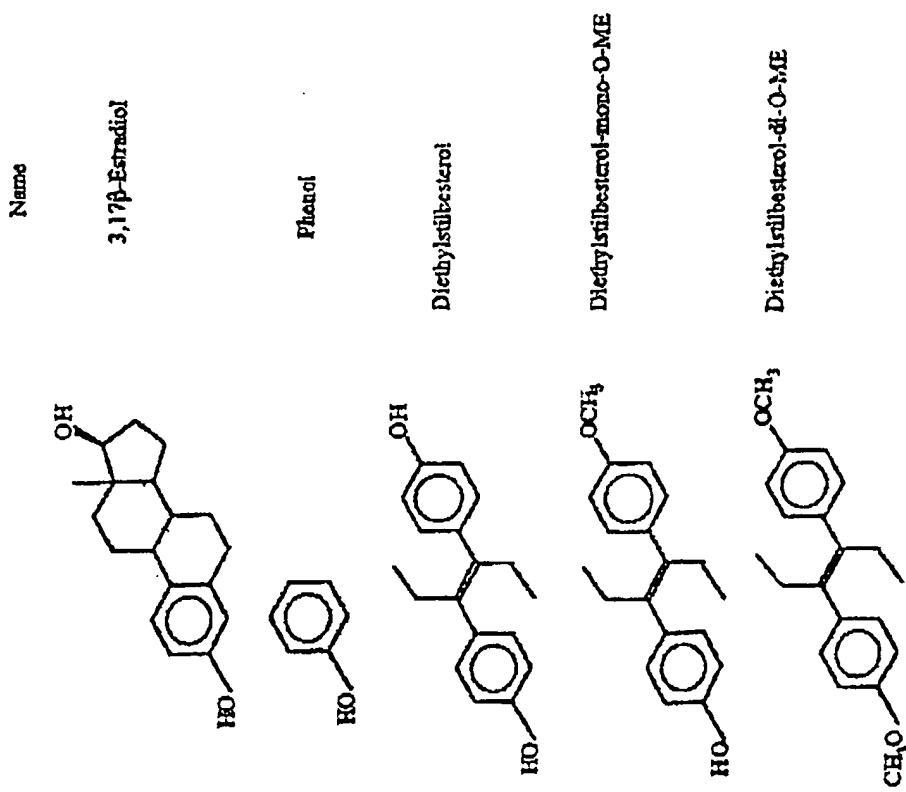


Figure 18

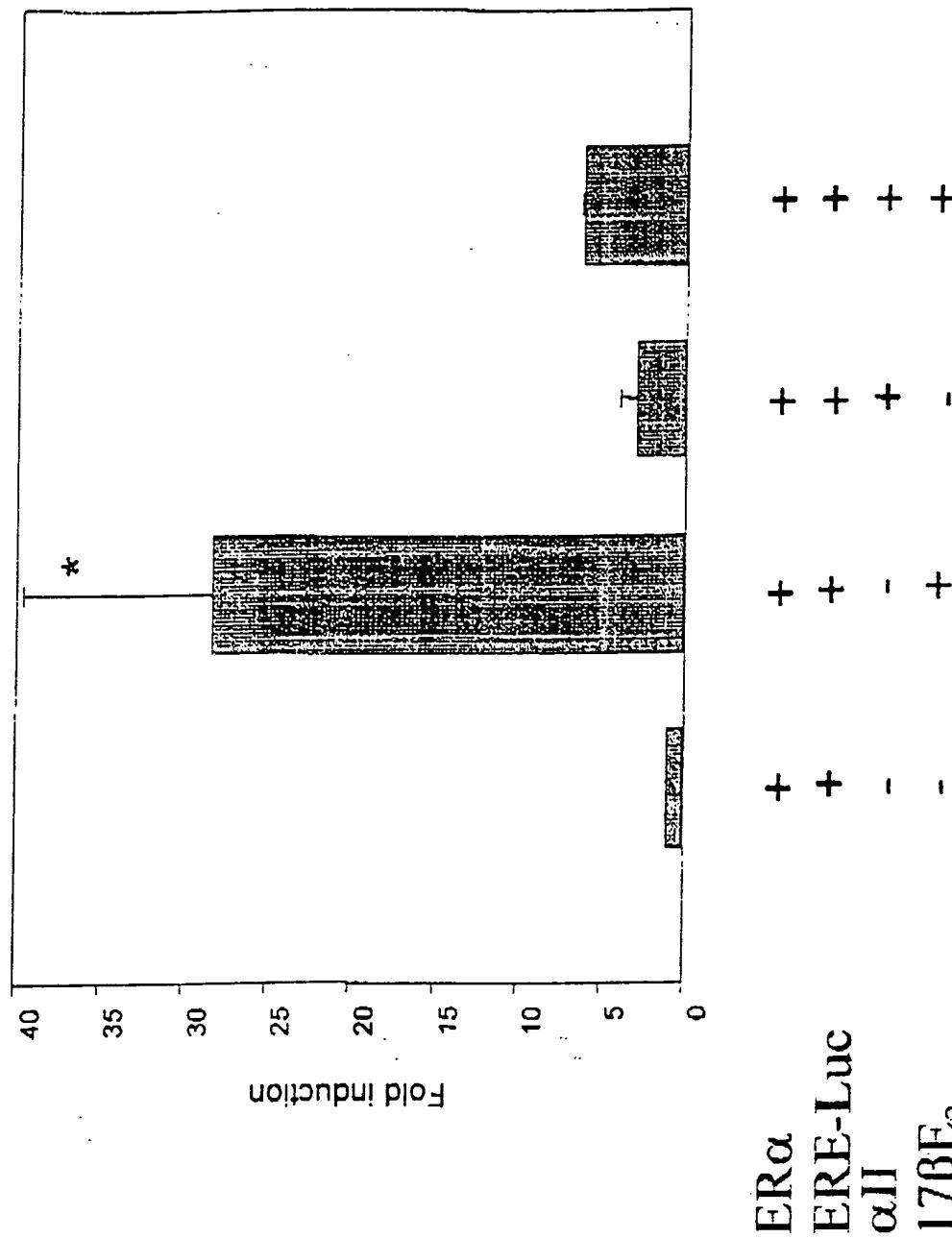


Figure 19: Effect of the all peptide on the 17 β E $_2$ -induced ERE activity in 293 cells

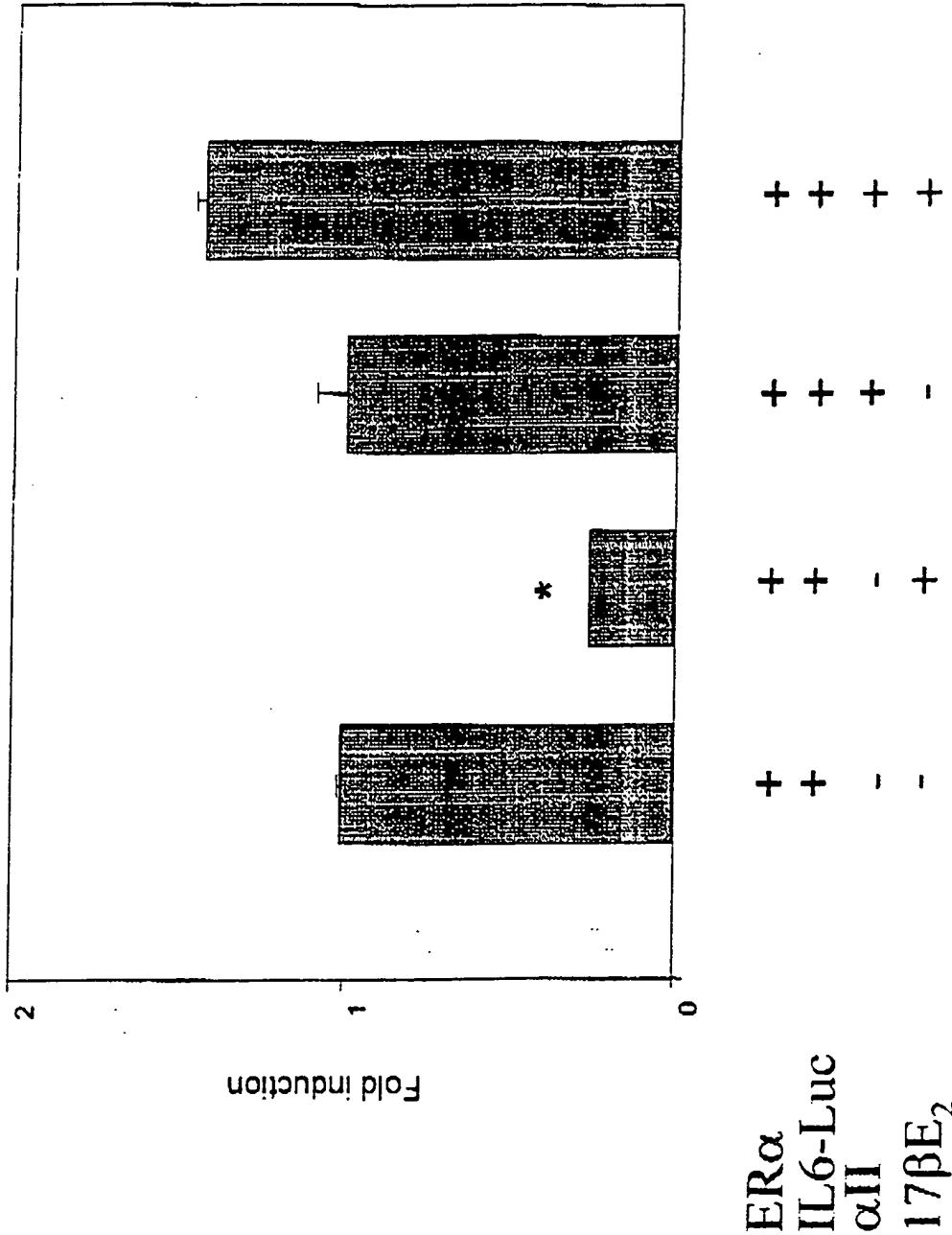


Figure 20: Effect of the all peptide on the 17 β E₂-induced inhibition of IL-6 activity in 293 cells

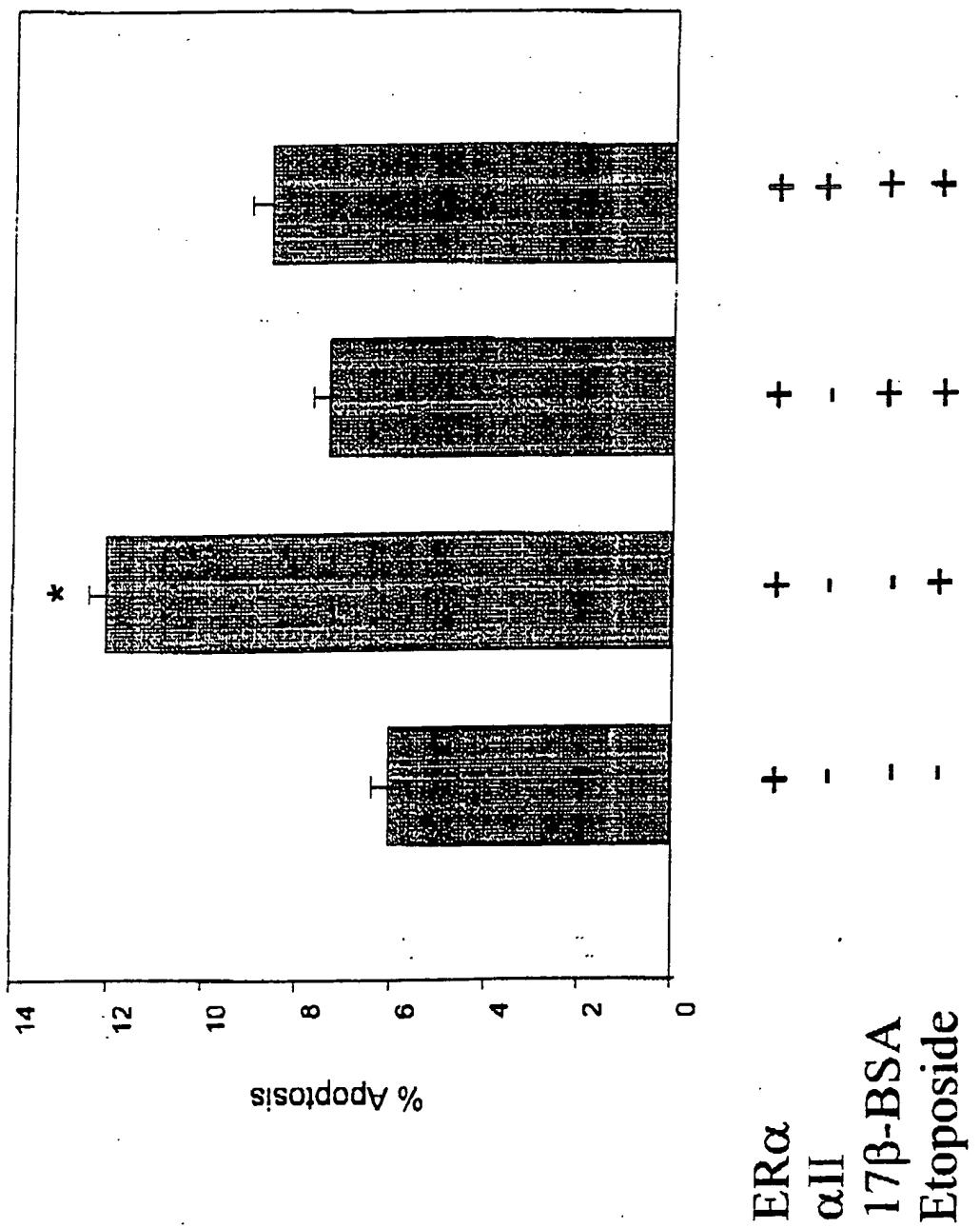


Figure 21: Effect of the all peptide on the Etoposide-induced apoptosis of 17b-BSA-activated 293 cells